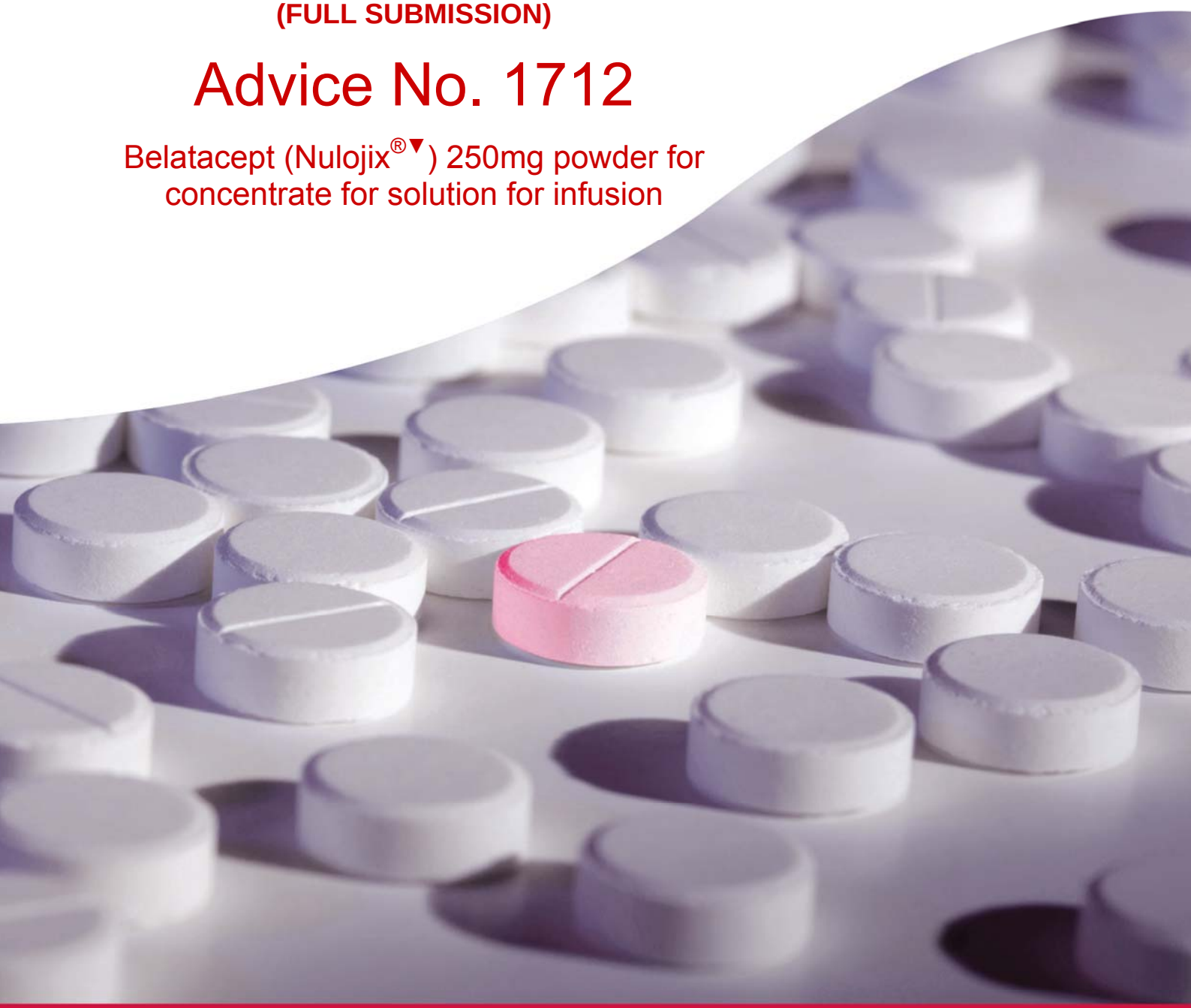
All Wales Therapeutics and Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

(FULL SUBMISSION)

Advice No. 1712

Belatacept (Nulojix®▼) 250mg powder for concentrate for solution for infusion



AWMSG Secretariat Assessment Report – Advice No. 1712
Belatacept (Nulojix®▼) 250 mg powder for concentrate for solution for infusion

This assessment report is based on evidence submitted by Bristol-Myers Squibb Pharmaceuticals on 30 January 2012[1].

1.0 PRODUCT DETAILS

Licensed indication under consideration	Belatacept, in combination with corticosteroids and a mycophenolic acid (MPA), is indicated for prophylaxis of graft rejection in adults receiving a renal transplant. It is recommended to add an interleukin (IL)-2 receptor antagonist for induction therapy to this belatacept-based regimen[2].
Dosing	Belatacept should be administered as an intravenous infusion at a relatively constant rate over 30 minutes. Refer to the Summary of Product Characteristics (SPC) for instructions on reconstitution and dilution of belatacept. The recommended dose is 10 mg/kg during the initial phase and 5mg/kg during the maintenance phase. Refer to the SPC for details of treatment frequency during each phase[2].
Marketing authorisation date	17 June 2011[2].

2.0 DECISION CONTEXT

2.1 Background

Kidney transplantation is preferable to dialysis for patients with end stage renal disease because it gives improved survival rates and quality of life[3]. Transplant patients must receive immunosuppression throughout the life of the grafted organ. Current immunosuppressants, such as the calcineurin inhibitors, ciclosporin (introduced in the 1980s) and tacrolimus (introduced in the 1990s), give low amounts of acute rejection in the short term, but in the long term can cause nephrotoxicity, hypertension and diabetes[3,4]. Data for the renal transplant centre at University Hospital of Wales, Cardiff, in 2009 shows that for recipients of deceased donors the rates of patients surviving with a functioning kidney transplant were 94% after 1 year and 85% after 5 years[5]. The aim of new immunosuppressants used in renal transplantation is to reduce acute rejections, improve longer term renal function and cardiovascular condition, and avoid new onset diabetes after transplant[3,4].

Belatacept acts by binding to specific antigen sites which prevent activation of T cells. If the T cells are inactivated the inflammatory response is prevented and rejection of the grafted kidney is avoided. Belatacept is administered intravenously; ciclosporin and tacrolimus are taken orally.

In 2009 there were 1,197 people living in Wales with kidney transplants, and 2,600 new transplants were conducted in the UK[5]. In 2010/11, 129 patients in Wales received a kidney transplant[1] (see section 5.1.1 for more detail).

Epstein-Barr (EBV) is the virus responsible for mononucleosis (glandular fever) and approximately 90% of adults have been exposed to the virus; hence are EBV seropositive. The remaining 10% of patients who are Epstein-Barr virus (EBV) seronegative however are not eligible to receive belatacept[1]. This is because belatacept-treated transplant recipients who are EBV seronegative are at an increased risk for post transplant lymphoproliferative disorder (PTLD) compared with those who are EBV positive.

Company-sought opinion suggests that belatacept would initially be used in transplant patients who are most at risk of an early decline in renal function. Predictors of poor renal function in the first year include recipients of extended criteria donor (ECD) kidneys, and also those receiving donation after cardiac death (DCD) kidneys. Of the total of 129 patients mentioned previously, 25 had a eGFR ≤ 30 ml/min/1.73m^2 at 1-year post transplant. The company consider such patients to be those who are at high risk of rejection in the first year[1] and therefore the most relevant population to receive belatacept in Wales. Potentially however the medicine could also be used on all EBV seropositive new transplant patients and EBV seropositive patients with existing transplants.

2.2 Comparators

The comparators requested by the Welsh Medicines Partnership (WMP)* were ciclosporin and tacrolimus (Advagraf®).

2.3 Guidance and related advice

- National Institute for Health and Clinical Excellence (NICE). Technology Appraisal 85. Immunosuppressive therapy for renal transplantation in adults (2004)[6].

The All Wales Medicines Strategy Group (AWMSG) has previously issued a recommendation for the use of tacrolimus (Advagraf®):

- Tacrolimus (Advagraf®) is recommended as an option for restricted use within NHS Wales for the prophylaxis of transplant rejection in adult kidney or liver allograft recipients.
- Tacrolimus (Advagraf®) is not recommended for use within NHS Wales for the treatment of allograft rejection resistant to treatment with other immunosuppressive medicinal products in adult patients.
- Tacrolimus (Advagraf®) should be prescribed by brand name to reduce the risk of medication errors.
- AWMSG is of the opinion that tacrolimus (Advagraf®) may be suitable for shared care for the above indication[7].

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

The company submission compared belatacept and ciclosporin for the immunosuppression of renal transplants using evidence from two phase III randomised controlled trials, BENEFIT and BENEFIT-EXT, which are discussed in section 3.1. BENEFIT and BENEFIT-EXT were of similar design and enrolled a broad range of renal transplant recipients and donor types. BENEFIT included recipients of standard criteria donor transplants while BENEFIT-EXT included recipients of ECD kidneys. Both were three year studies with primary endpoints assessed at 12 months.

* In April 2012 the Welsh Medicines Partnership became part of the All Wales Therapeutics and Toxicology Centre (AWTTC).

At the end of the three year treatment period patients could elect to enter a long-term extension study.

The company was not able to provide a direct comparison of belatacept and tacrolimus, but provided an indirect comparison obtained using a network meta-analysis of trials comparing tacrolimus with ciclosporin and trials comparing belatacept with ciclosporin. This indirect comparison is discussed in section 3.2.

3.1 The effectiveness of belatacept in comparison with ciclosporin

The two phase III trials of belatacept were carried out on adult renal transplant patients with ciclosporin as the comparator. The trials have been published in peer reviewed publications for both the 12 month and 36 month endpoints.[8–11] The first trial, BENEFIT[9,10], was conducted using recipients of standard criteria donor kidneys, where the kidney grafts were received either from living donors or from deceased donors with an anticipated cold ischemia time of less than 24 hours. The second trial, BENEFIT-EXT[8,11], was conducted on recipients of ECD kidneys, where the transplants were from donors aged 60 years or over, donors aged over 50 years with serious illness and donors suffering cardiac death.

For both trials patients were randomised 1:1:1; the first group received a less intensive (LI) belatacept regimen, the second group received a more intensive (MI) belatacept regimen, and the third group received ciclosporin. The regimens used for the three treatments are given in Table 1 below. The LI regimen reflects the licensed indication for belatacept; results for the MI regimen will therefore not be considered further in this report. Patients were not blinded as to which treatment they received because dose monitoring was required for ciclosporin but not for belatacept.

Table 1: Regimens used for BENEFIT and BENEFIT-EXT[1]

Treatment	Regimen
Belatacept(LI)	10 mg/kg IV on days 1 and 5, and then every 2 weeks through month 1 (weeks 2 and 4), and every 4 weeks through to Month 3 (weeks 8 and 12). After 3 months, patients received the maintenance dose of belatacept 5 mg/kg administered every 4 weeks until completion of the trial at Month 36.
Belatacept(MI)	10 mg/kg IV on days 1 and 5, then every 2 weeks through month 3 (weeks 2, 4, 6, 8, 10, and 12), and then every 4 weeks through 6 months (weeks 16, 20, and 24). After 6 months, patients received the maintenance dose of belatacept 5 mg/kg administered every 4 weeks until completion of the trial at Month 36.
Ciclosporin	Ciclosporin twice daily to achieve a trough serum target of 150-300 ng/mL the first month and 100-250 ng/mL thereafter.

The primary endpoints for both BENEFIT and BENEFIT-EXT at 12 months were the proportion of patients surviving with a functioning graft and those meeting the composite renal impairment measurement. Composite renal impairment was defined as a glomerular flow rate (GFR) less than 60 ml/min/1.73m^2 or a decrease in GFR of greater than 10 ml/min/1.73m^2 between month 3 and month 12 after transplant. Incidence of acute rejection was also a primary endpoint in the BENEFIT trial at 12 months. Kidney function at 36 months was not determined by direct measurement of GFR. Instead, GFR was calculated using measurements of the creatinine levels of the blood and urine together with a model to calculate GFR[1,12].

3.1.1 BENEFIT results

Participants in the BENEFIT trial were end stage renal disease patients aged 18 years or over who had not previously had a kidney transplant (*de novo*). The mean age of trial participants was 43 years and approximately 70% of the participants were male. Patient ethnicities were 60% white, 12% black and 9% Asian[1].

Results for the primary endpoints at 12 months and key endpoints at 12 and 36 months are shown in Table 2. Figures for survival of the patient and graft at 12 months and 36 months were comparable for the belatacept and ciclosporin treatment arms. The number of patients meeting the composite renal impairment endpoint at 12 months following transplant was significantly greater for ciclosporin treated patients than for those receiving belatacept ($p < 0.0001$); however, belatacept-treated patients had a significantly higher chance of acute rejection: 17% (39 of 226 patients) in the first 12 months for belatacept compared to 7% for ciclosporin (16 of 221 patients). Most of the acute rejections for belatacept-treated patients occurred within the first three months following transplant. Despite the higher acute rejection rate with belatacept, most patients were remediated using corticosteroids and T cell depletion treatment, such that their kidney function improved. Furthermore, the difference between the numbers of patients experiencing acute rejection at 12 months did meet the 20% non-inferiority margin. The 36 month data shows the same trend as the 12 month data, with belatacept-treated patients having a higher acute rejection rate but superior kidney function (the difference in the mean calculated GFR was significantly higher [$p < 0.0001$] when compared with ciclosporin-treated patients). The higher incidence of acute rejection did not lead to lower overall survival rates at 36 months for belatacept compared to ciclosporin[10].

Table 2. Endpoints at 12 months[10] and 36 months[9] for BENEFIT

	Belatacept (n = 226)	Ciclosporin (n = 221)
Patients surviving 12 months with a functioning graft n (%)	218 (97)	206 (93)
Deaths at 12 months n (%)	4 (2)	7 (3)
Acute rejection at 12 months n (%)	39 (17)	16 (7)
Patients meeting composite renal impairment endpoint at 12 months* ($p < 0.0001$)	116 (54)	166 (78)
Patients surviving 36 months with a functioning graft n (%)	208 (92)	196 (89)
Death at 36 months n (%)	10 (4)	15 (7)
Acute rejection at 36 months n (%)	39 (17)	21 (10)
Mean calculated GFR ml/min/1.73 m^2 (standard deviation) at 36 months ($p<0.0001$)	66 (27)	44 (24)
*defined as GFR < 60 mL/min/1.73 m^2 or decrease of GFR of > 10 mL/min/1.73 m^2 between months 3 to 12.		

In the BENEFIT trial the death rate after 36 months was similar for both treatment groups (4% [10 of 226 patients] for belatacept versus 7% [15 of 221 patients] for ciclosporin). PTLD, lymphoma of the immune system caused by infection with the Epstein Barr virus) occurred for two belatacept patients and only one ciclosporin-treated patient. Common serious adverse effects, which occurred in similar numbers for both treatments, included urinary tract infections and cytomegalovirus infections[9,10].

3.1.2 BENEFIT-EXT results

In this trial patients also had end stage renal disease, were aged 18 years or over and had not previously had a kidney transplant. The patient population was similar to that in BENEFIT except that the patients were older, which reflects the patient population likely to receive an ECD kidney transplant[1].

The results of the primary endpoints (the number of surviving patients with a functioning graft and the number of patients meeting the composite renal impairment measure, both at 12 months) are shown in Table 3 along with other secondary endpoints at 12 months[8] and 36 months[11]. A total of 175 transplant patients received belatacept and 184 patients received ciclosporin. The proportions of patients surviving with a functioning graft at both 12 months and 36 months were comparable for the two treatments. The acute rejection rate was significantly higher for belatacept than for ciclosporin, but the difference in the acute rejection rate between belatacept treated patients and ciclosporin-treated patients met the 20% non–inferiority criteria at 12 months. Most of the acute rejections for belatacept-treated patients occurred within the first three months following transplant. The number of patients meeting the composite renal impairment endpoint at 12 months following transplant was greater for ciclosporin-treated patients than for belatacept-treated patients ($p = 0.066$)[8].

The 36 month mean calculated GFR values were higher for belatacept-treated patients than for ciclosporin-treated patients. The acute rejection rate at 36 months was higher for belatacept-treated patients than for ciclosporin-treated patients.

Table 3. Endpoints at 12 months[8] and 36 months[11] for BENEFIT-EXT

	Belatacept (n = 175)	Ciclosporin (n = 184)
Patients surviving 12 months with a functioning graft n (%)	155 (89)	156 (85)
Deaths at 12 months n (%)	4 (2)	8 (4)
Acute rejection at 12 months n (%)	31 (18)	26 (14)
Patients meeting composite renal impairment endpoint at 12 months* n (%) (p = 0.066)	130 (77)	151 (85)
Patients surviving 36 months with a functioning graft n (%)	144 (82)	147 (80)
Deaths at 36 months n (%)	15 (9)	17 (9)
Acute rejection at 36 months n (%)	**	29 (16)
Mean calculated GFR ml/min/1.73m^2 (standard deviation) at 36 months	42 (25)	32 (22)
*defined as GFR < 60 mL/min/1.73 m^2 or decrease of GFR of >10 mL/min/1.73 m^2 between months 3 to 12.		

In BENEFIT-EXT the percentage death rate after 36 months was the same for both treatment groups (belatacept: 9% [15 of 175 patients] versus ciclosporin: 9% [17 of 174 patients]). The incidence of new onset diabetes after transplant was 10% [13 of 175 patients] for belatacept-treated patients and 9% [11 of 184 patients] for ciclosporin-treated patients after 36 months. As also seen in the BENEFIT trial common serious adverse effects, which occurred in similar numbers for both treatments, included urinary tract infections and cytomegalovirus infections[11].

3.2 The effectiveness of belatacept in comparison with tacrolimus

The applicant company were unable to supply any evidence providing a direct comparison between belatacept and tacrolimus; and literature searches by AWTTC have not identified any such evidence. As part of the company submission, a network meta analysis was conducted to obtain an indirect comparison of treatments[1]. The meta-analysis used 32 studies; 29 comparing tacrolimus with ciclosporin and three comparing belatacept and ciclosporin (two of these three being the studies discussed in section 3.1.1, BENEFIT and BENEFIT-EXT). The results, which were provided but remain confidential, showed no significant difference between belatacept and tacrolimus treatments for mortality, graft loss, or GFR at either the 12 month or 36 month interval. The acute rejection rate of belatacept was significantly higher for belatacept compared with tacrolimus and the incidence of new onset diabetes after transplantation was lower for belatacept than for tacrolimus.

3.3 AWTTC critique

- Non-inferiority was demonstrated for the composite endpoint of patient and graft survival in both pivotal studies, in spite of more episodes of acute rejection with belatacept treatment.
- The Committee for Medicinal Products (CHMP), considered the BENEFIT-EXT trial, with subjects at a greater risk of graft failure, to appear to be more relevant for European renal transplant patients in general[13]. CHMP state that the three year data for renal function in the BENEFIT-EXT trial shows a clinically meaningful difference in favour of belatacept compared to ciclosporin[13].
- Renal function in the first year after transplant is considered an important factor influencing long term graft survival[14] and the probability of cardiovascular death[15]. In addition the three year renal function results are expected to result in better survival rate for belatacept treated patients compared to ciclosporin treated patients. However, further data is required to confirm that belatacept shows improved long term survival rates compared to other immunosuppressive drugs such as the CNIs.
- Both phase III trials showed differences in blood pressure in favour of belatacept but this was only statistically significant in the BENEFIT trial at 12 months. In both trials however belatacept treated patients had a significantly reduced chance of requiring anti-hypertensive medication than ciclosporin patients (50% reduction p=0.002 in BENEFIT and 40% reduction (p=0.02) in BENEFIT-EXT). There was little difference in new onset diabetes post transplant between belatacept and ciclosporin at 36 months in either the BENEFIT or the BENEFIT-EXT trial (see section 3.1.2).
- The acute rejection rate in the first three months is significantly greater for belatacept than for ciclosporin or tacrolimus[1], although it should be noted that most patients suffering acute rejection were remediated. Nevertheless an increased number of acute rejections would increase the need for more patient intervention and additional immunosuppressive treatment[13].

- Belatacept, like other immunosuppressives, increases the risk of malignancies and infections. Belatacept-based regimens are associated with some specific safety issues such as PTLD, which was significantly more common with belatacept than with ciclosporin. Such risks however are addressed in the SPC[2] and in the risk management plan[13].
- The first three months of belatacept administration following transplant would be in hospital; from month four administration of belatacept would be in the patient's own home or via a homecare nursing service[1].

4.0 SUMMARY OF THE EVIDENCE ON COST-EFFECTIVENESS

4.1 Context

The company submission[1] describes a cost utility analysis of belatacept in its licensed indication for the prophylaxis of graft rejection in adults receiving a renal transplant, in combination with corticosteroids and mycophenolic acid (MPA)[2]. The comparators used are ciclosporin and tacrolimus, each as part of an immunosuppressive regimen. The analysis is based on a Markov state transition model, assuming four health states: 'functioning graft', 'failed graft', 'functioning re-graft' and death.

Patients entering the functioning graft health state are categorised by four GFR states, corresponding to GFR stages 2, 3a, 3b and 4 (as defined in Appendix 1 Table 1B) based on the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) classification. The base case analysis utilises 36-month pooled data from the BENEFIT and BENEFIT-EXT trials of belatacept versus ciclosporin.

Due to a lack of direct comparative data, an indirect meta-analysis provides parameter values for tacrolimus relative to belatacept. Transition probabilities for the Markov model are derived from risk equations based on data from the United States Renal Data System (USRDS). Non-drug resource use and costs, and utility values for weighting health states, are derived largely from Welsh-specific sources. The model assumes a 40-year time horizon to represent life time in the base case[1]. See Appendix 1 for further details.

4.2 Results of the base case analysis

Results of the base case analysis are presented in Table 4[1]. Treatment with belatacept is estimated to be more costly and more effective when compared with both ciclosporin and tacrolimus. The key drivers of the cost estimates are immunosuppression costs, and costs associated with graft failure, including dialysis and re-transplantation. The key drivers of outcomes are the modelled differences in GFR, which determine the duration of functioning graft for each immunosuppressant regimen.

Table 4. Company reported results of the base case cost utility analysis[1].

	Belatacept	Ciclosporin	Difference	Tacrolimus	Difference
Immunosuppression costs	£129,429	£19,729	£109,701	£20,124	£109,306
Dialysis costs	£100,376	£143,524	-£43,148	£128,633	-£28,258
GFR costs	£25,562	£19,453	£6,109	£20,723	£4,838
Re-transplant costs	£27,458	£37,812	-£10,354	£34,595	-£7,137
NODM costs	£1,429	£1,709	-£281	£3,557	-£2,128
AR costs	£320	£220	£100	£145	£175
PTLD costs	£64	£17	£47	£19	£45

	Belatacept	Ciclosporin	Difference	Tacrolimus	Difference
Total discounted costs	£284,638	£222,465	£62,173	£207,797	£76,841
Total discounted Life Years	13.85	11.31	2.55	11.41	2.44
Total discounted QALYs	6.95	4.99	1.96	5.24	1.71
Incremental cost per LYG			£24,405		£31,475
ICER (£/QALY gained)		**£31,741**		**£44,862**	

GFR = glomerular filtration rate; NODM = new onset diabetes mellitus; AR = acute rejection; PTLD = post-transplant lymphoproliferative disorder; LYG = life years gained; QALY = quality-adjusted life-year; ICER = incremental cost effectiveness ratio.

A wide range of one way sensitivity analyses have been conducted. These indicate that the ICERs for comparison against both ciclosporin and tacrolimus are sensitive to the assumed hazard ratio for graft failure: removal of the assumed differential cardiovascular and metabolic effects increases the ICERs to £38,928 per QALY gained and £56,101 per QALY gained, respectively. The comparison with ciclosporin is next most sensitive to changes (±25%) in the cost of dialysis (ICERs ranging from £26,300 to £37,200). The ICER for the comparison with tacrolimus is most sensitive to the time horizon (10-year ICER = £63,200).

The impacts of the patient survival equations, discount rates, utility and other cost estimates have all been explored, with ICER estimates within these ranges. Results of probabilistic sensitivity analysis (PSA) have not been provided by the company.

In scenario analyses, restricting the use of belatacept to patients with diabetes reduced the ICER to £19,000 per QALY gained, and use only in patients with kidneys received from standard criteria donors (SCD) increased the ICER to £35,000 per QALY gained versus ciclosporin. Using home administration for belatacept (via a home care nursing service) is reported to reduce the ICERs compared to both ciclosporin (£20,100/QALY gained) and tacrolimus (£31,600 per QALY gained).

4.3 AWTTC critique

It is unclear that the base case models would provide the most plausible estimates of the cost effectiveness of belatacept in clinical practice, as there appears to be significant uncertainty in key efficacy assumptions and parameter values. It is plausible that the estimated ICERs could exceed those reported when used in practice.

Strengths of economic evidence include:

- Direct comparative data are available to model efficacy for both belatacept and ciclosporin.
- In the absence of direct comparative data for tacrolimus, relative efficacy estimates were derived from a well conducted network meta-analysis.

Limitations of the economic evidence include:

- Despite company predictions that belatacept will be targeted at transplant patients who are in receipt of extended criteria donor (ECD) kidneys, the company has not provided analyses specific to this subgroup.
- The BENEFIT trial was conducted in patients at an unusually low risk of graft failure[16]; CHMP noted that subjects enrolled in the BENEFIT-EXT trial, who had a greater risk of graft failure, are more representative of patients in practice[13].

The base case model is reported to use belatacept data from both the BENEFIT and BENEFIT-EXT trials, alongside the data from the indirect meta-analysis. It is unclear how these data are employed in the base case model alongside that from the indirect meta-analysis, when they form part of the indirect meta-analysis. Use of all data from the indirect meta-analysis, or from just the BENEFIT/BENEFIT-EXT trials, dramatically increases the ICERs.

- The baseline recipient and donor characteristics are based on US data, rather than UK- or Wales-specific data. The risk equations used to model the impact of GFR on long term outcomes are based on US data, which appear to overestimate the risks of graft failure compared with international observational data[17].
- In addition to these uncertainties, the company asserts that belatacept will improve graft survival based in part on a reported improvement in cardiovascular (i.e. blood pressure and lipid effects) and metabolic effects (i.e. development of new onset diabetes post transplant). A constant hazard ratio for graft failure (of 0.85) in favour of belatacept has been applied, but the assumptions around this hazard ratio appear to be based on inconsistent evidence from the BENEFIT/BENEFIT-EXT trials: there was no significant difference in cardiovascular and metabolic effects between belatacept and ciclosporin by 36 months in the most relevant trial. The model is sensitive to the value of this hazard ratio.
- There is a lack of transparency in some of the key cost parameters.
- Although not reported by the company, AWTTC analysis using the company's model appears to indicate that belatacept is more cost effective than ciclosporin only when the willingness to pay exceeds around £35,000/QALY gained, and is more cost effective than tacrolimus only when the willingness to pay exceeds around £75,000/QALY gained. The company notes that the cost effectiveness of belatacept will vary depending on the individual patient type, and suggests that belatacept could be more cost effective or even cost saving in patients with ECD kidneys and low post transplant GFR; however, no such analyses have been provided by the company.

4.4 Review of published evidence on cost-effectiveness

Standard literature searches conducted by AWTTC have not identified any published evidence on the cost effectiveness of belatacept within its current licensed indication.

5.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

5.1 Budget impact evidence

5.1.1 Context and methods

Based on prevalence data from the UK Renal registry[5] the company report that there were 1,197 renal transplant patients in Wales in 2009. The number of transplants conducted in Cardiff in 2010/2011 was reported to be 129 (figure not verified). This figure was taken to represent the yearly incidence of renal transplants in Wales over the coming 5-year period, resulting in an estimated 645 incident kidney transplants.
Mortality estimates were taken from the economic model submitted by the company and estimated that 47 of these 645 patients would die, resulting in a net number of 598 patients within the five year period. Of these patients, those who are Epstein-Barr virus seronegative (estimated by the company to be approximately 10%) will not be eligible to receive belatacept.

Based on company-sought expert opinion, belatacept would be used in patients who are at most risk of an early decline in renal function, as predicted by being recipients of ECD kidneys including recipients of DCD kidneys. Based on expert opinion, the

company reported that the number of patients meeting this criteria during 2010-2011 was 40 patients, of whom 25 had GFR less than or equal to 30 ml/min/1.73m^2 at one year post-transplant. Thus, 25 incident cases per year were predicted to initiate belatacept. The company therefore takes cumulative net five-year costs obtained from the cost effectiveness model (split into event and therapy related costs) and averages these to provide an expected annual cost, assuming that 25 incident cases will receive belatacept in each of the five years (2012–16).

5.1.2 Company-reported budget impact analysis[1]

Table 5. Company reported results of budget impact analysis

	Year 1 (2012)	Year 2 (2013)	Year 3 (2014)	Year 4 (2015)	Year 5 (2016)
Number of patients initiating belatacept in each year	25	25	25	25	25
Administration and monitoring costs	£231,430	£462,860	£694,290	£925,720	£1,157,150
Primary care costs	0	0	0	0	0
Secondary & tertiary care costs	-£94,085	-£188,170	-£282,255	-£376,340	-£470,425
Staffing	0	0	0	0	0
Infrastructure	0	0	0	0	0
Personal social services	0	0	0	0	0
Overall net cost for whole population	£137,345	£274,690	£412,035	£549,380	£686,725

5.1.3 AWTTC critique of the budget impact analysis

- The company has made reasonable efforts to define the epidemiology of kidney transplantation using Welsh-specific data although only one centre in Cardiff was considered, which may not take into account patients residing in North Wales who may receive their health care in the North West of England.
- The budget impact calculations are based solely on a subset of patients, who are the recipients of CDC kidneys who had GFR ≤ 30 ml/min/1.73 m^2, while the economic evaluation and clinical effectiveness data are presented for the whole population of patients covered by the licensed indication. If used in all EBV-positive patients meeting the licensed indication, the number of patients could be substantially greater than estimated by the company.
- The analysis presented by the company assumes that the number of incident patients eligible for belatacept treatment will remain constant over the period of five years. This is in contrast to a company-reported increase in the annual number of renal transplantations at the renal transplant centre at University Hospital of Wales, Cardiff.
- Collectively, there is considerable uncertainty in the company's budget impact estimates.

5.2 Table of comparative unit costs

According to NICE guidance on immunosuppressive therapy for renal transplantation in adults, the choice of calcineurin inhibitor should be individualised based on the side effect profile of each drug and its suitability for the individual patient[6]. Table 6 provides example acquisition costs based on the company's estimates of average doses used over the first year of treatment. Maintenance doses may differ over time based on factors such as body weight, blood concentrations, renal function and the use of concomitant agents. The first year cost estimates below are therefore indicative only.

Table 6. Examples of first year immunosuppressant acquisition costs for the prophylaxis of allograft rejection in adult kidney recipients

Regimen	Example of daily dose averaged over first year	Approximate first year cost[18]
Ciclosporin (Capsorin®) capsules 25, 50, 100mg	270 mg	£1,675
Ciclosporin (Neoral®) capsules 10, 25, 50, 100mg	270 mg	£2,535
Tacrolimus (Advagraf®) prolonged-release capsules 0.5, 1, 3 and 5 mg	6.7 mg	£3,277
Tacrolimus (Prograf®) capsules 0.5, 1, 5 mg	6.7 mg	£4,300
Tacrolimus (Vivadex®) capsules 0.5, 1, 5 mg	6.7mg	£2,567
Belatacept (Nulojix®) 250 mg powder for concentrate for infusion	5–10 mg/kg given over 17 doses in first year	£14,180
Costs based on company estimates calculated for a 75 kg adult, using simple average of BNF no. 62 list prices for each available formulation line (excluding VAT)[18] Note: Different brands of the same agent may not be interchangeable. See all relevant Summaries of Product Characteristics for full dosing details. This table does not imply therapeutic equivalence of the stated drugs and doses.		

6.0 ADDITIONAL INFORMATION

6.1 Shared care arrangements

AWTTC is of the opinion that belatacept (Nulojix®▼) is suitable for specialist only prescribing within NHS Wales for the stated indication.

6.2 Ongoing studies

The company is conducting analysis of the four year data on the phase III trials for both BENEFIT and BENEFIT-EXT transplant patients. The clinical study reports will be provided to the AWMSG when available.

6.3 AWMSG review

This assessment report will be considered for review three years from the date of Ministerial ratification (as disclosed in the Final Appraisal Recommendation).

6.4 Evidence search

Date of evidence search: 10 February 2012
Date range of evidence search: No date limits were applied to database searches.

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Appendix 1. Additional health economic information

Table 1A. Health economic model detail[1]

	Base case model	Appropriate?
Comparator(s)	Belatacept intravenous infusion is compared against oral ciclosporin and oral tacrolimus.	Yes, as agreed by AWTTC. Sirolimus was not considered by the company to be a suitable comparator as its use is generally restricted to treating renal transplant patients whose renal function is steadily declining on ciclosporin or tacrolimus, and in whom other measures (such as dose adjustment) have not been successful.
Population	Adult kidney transplant recipients with a mean age of 46.5 years and an average body weight of 75 kg.	AWMSG appraises medicines within their licensed indication. The base case model considers all patients meeting the licensed indication for belatacept[2]. The company submission stressed that belatacept will be of most benefit to patients with increased risk of early decline in renal function who are recipients of extended criteria donor (ECD) kidneys, including recipients of donation after cardiac death (DCD) kidneys. However, no subgroup analysis has been provided for this suggested target patient population.
Model type and description	Cost utility analysis (CUA) based on a Markov model to extend beyond the trial time horizon. For the base case analysis, 36 month GFRs, observed from network meta analysis of relevant trials, are used to predict long term probability of graft failure, re-transplantation and death. In addition to death the model has three other health states: functioning graft (in which patients are classified into four groups based on their GFR at the end of the observation period), dialysis/graft failure and re-transplantation/new graft. Survival functions are used to obtain the transition probabilities for the Markov model. The parameters for these survival functions are based on risk equations fitted in the PORT study on the USA Renal Data System data. Occurrence of acute rejection (AR), new onset diabetes mellitus (NODAT) and post transplant lymphoproliferative disorder (PTLD) are also included in the model. An annual cycle length is employed.	Yes. CUA is the preferred type of analysis. The choice of GFR as a proxy for renal function and progression to dialysis and re-transplantation is well founded. The company reports that cardiovascular disease (CVD) risk was not included in the model, due to a lack of appropriate data, but refer to the efficacy section below. The risk equations used in the model were derived from a large USA database-based study.
Perspective	NHS Wales	Yes.
Time horizon	An analytical time horizon of 40 years is assumed, taken to represent lifetime for a transplant patient with a mean age of 46.5 years at transplantation. Ten and 60 year time horizons are explored in sensitivity analyses.	It is appropriate to use a lifetime analytical time horizon given the life-long nature of the condition. The model is sensitive to the assumed time horizon for the comparison of belatacept and tacrolimus, with lower time horizons increasing the ICER.
Discount rate	3.5% discount rate for costs and outcomes, with 0% and 6% explored in sensitivity analyses.	Yes.

	Base case model	Appropriate?
Efficacy	For the observation period, treatment responses are derived from the pooled BENEFIT and BENEFIT-EXT trials and a network meta-analysis conducted on trials comparing immunosuppressant therapies in adult transplant patients, to enable comparison against tacrolimus. Efficacy estimates used in the model were derived using Weibull and exponential survival functions whose parameters were derived using risk equations fitted in the PORT study. The survival functions use information on patient and donor characteristics, GFR and the occurrence of AR, PTLD and NODAT. Constant transition probabilities are assumed for the transition from dialysis to re-transplantation and death and from re-transplantation to dialysis or death. Time dependent transition probabilities were applied for transitions from functioning graft to both dialysis and death. A hazard ratio of 0.85 is assumed for graft failure and survival to account for trial-observed differences in cardiovascular and metabolic parameters (i.e. lipids, blood pressure and development of NODAT).	There are a number of limitations and significant uncertainty related to the efficacy data. Efficacy estimates for the initial observation period were derived from the trial data and a network meta-analysis of randomised controlled trials of belatacept, ciclosporin and tacrolimus. The BENEFIT and BENEFIT-EXT trials of belatacept included different patient populations, the former being considered by CHMP to be at an unusually low risk of graft failure compared to those seen in routine practice[13], and it is unclear that combined data from both trials would adequately reflect clinical effectiveness in the target population. The classification of GFR at 36 months is used to estimate time dependent probabilities of graft failure, based on risk equations derived from US data. A validation study applying these equations to an international data set indicates that the predicted risk using these equations was higher than the observed risk in all but those with the lowest level of risk for graft failure[17]. The assumed characteristics of donors and recipients are also based on the US cohort data. The risks of graft failure would therefore appear to be a source of uncertainty, and the model is particularly sensitive to these. In addition, a hazard ratio for belatacept versus calcineurin inhibitors has been applied to graft and patient survival equations to "accommodate potential benefits associated with less nephrotoxicity and superior cardiovascular and metabolic profile"[1]. However, differences in blood pressure, lipid parameters and development of new onset diabetes after transplant (NODAT) were inconsistent between the pivotal belatacept trials by 36 months: the most relevant of the trials (BENEFIT-EXT) observed no statistically significant differences between belatacept and ciclosporin for these cardiovascular and metabolic effects. The value of 0.85 is based on a simple assumption, and there appears little evidence to support its application for the duration of the model. Sensitivity analysis demonstrates the model is sensitive to the assumed value of this hazard ratio. A hazard ratio of the effect of NODAT on graft failure and on death is reported in the submission as being based on published sources, but no reference has been given and it has not been possible for AWTTC to verify this. In the base case model, the source of the observational period parameters (36 months in the base case model) are reportedly based on the network meta-analysis with belatacept inputs from the trials.

	Base case model	Appropriate?
Efficacy		When the observational period parameters are based only on the network meta-analysis data (of which the belatacept trial data are incorporated), the ICERs increase dramatically to £47,538 per QALY gained and £70,715 per QALY gained for comparison against ciclosporin and tacrolimus, respectively. The method of estimating and incorporating 36 month GFR for the drugs seems to have a substantial impact on model outputs.
Adverse effects	The model incorporates the incidence of AR, NODAT and PTLD in BENEFIT and BENEFIT-EXT trials in the observation period. The impact of these adverse events on long term outcomes in the model was also considered through converting the published hazard ratios for effect of NODAT on graft failure and death to Weibull parameters. Cardiovascular risk was reportedly not considered in the model.	Adverse event rates are based on the trial data for a maximum follow up period of 36 months. It appears that disutility associated with their incidence is applied for the entire cycle length of one year. It is unclear how adverse events have been considered beyond this 36 month period within the model. Additionally, some common adverse events related to the use of belatacept were not considered, such as the occurrence of TB and infections.
Utility values	Utility estimates were based on a published study in which data on health related quality of life were collected from patients undergoing kidney transplant at the renal unit at the University Hospital of Wales, Cardiff (n = 144) and combined with data collected from Saint Louis University Hospital, St Louis, MO (n = 137)[19]. The instrument used in the study was EQ-5D. The study also estimated the disutilities associated with NODAT, AR and PTLD. The values of the utilities used were varied in sensitivity analysis.	Yes. Utility data were collected from Welsh patients using EQ-5D, which is the preferred generic preference based measure. However, it is not possible to verify the disutility assumed for adverse events. One way sensitivity analysis exploring different values of these utilities/disutilities showed that the results are relatively insensitive to these values.
Resource use and costs	Immunosuppressant drug acquisition costs were based on BNF 2011 prices and calculated assuming an average body weight of 75 kg. The dosages were based on clinical practice in Cardiff as reported in the PORTRAIT study, which is a retrospective observational study of transplant patients managed at the renal transplant unit in Cardiff[16]. Cost estimates were also derived from the same study for outpatient attendances, lab tests, monitoring, hospitalisations and all renal related post-transplant events. Adverse event costs (PTLD, NODAT and AR) are derived from other published sources.	Yes. The PORTRAIT study was conducted in a single centre in Cardiff and although it is possible that it does not reflect current resource use and costs in other relevant centres in the UK, would seem a good source of these data. It is not clear whether the prices applied to the resources used were all inflated to 2011 values. Some possibly relevant costs may not have been included in the model including the cost of the background immunosuppressive regimen and screening to identify the EBV and TB status. There is a lack of transparency in relation to some of the composite cost parameter values that have been assumed.

	Base case model	Appropriate?
Uncertainty	A range of one-way sensitivity and scenario analyses has been conducted. No probabilistic sensitivity analyses have been reported in the submission.	One way sensitivity analyses indicate that the comparison with ciclosporin is most sensitive to the cost of dialysis, which when increases improves the cost effectiveness of belatacept compared with ciclosporin. The comparison with tacrolimus is most sensitive to the time horizon, where shorter time horizon of 10 years is associated with an ICER of £63,185, and the belatacept hazard ratio of graft failure, where a hazard ratio of 1 (assuming no differential effects of belatacept versus tacrolimus in relation to CVD and metabolic impacts on graft or patient survival) results in an ICER of £56,101. All the reported one way sensitivity analyses indicate that belatacept is more effective and more costly compared with both ciclosporin and tacrolimus. The company has stated in its submission that belatacept will be targeted at patients with poor post-transplant renal function and increased likelihood of a rapid progression to graft failure (i.e. ECD recipients), but has not provided analyses to reflect this use. The base case relates to a mixed population (SCD and ECD) and a scenario analysis has been conducted in SCD recipients only. The company has not reported the results of any PSAs within its submission. AWTTC analysis using the company's model appears to generate a mean ICER estimate of £47,600 (95% CI £27,824–87,166) for belatacept versus ciclosporin and £70,598 (95% CI £37,011–171,846) versus tacrolimus. The multiway CEAC appears to suggest that belatacept would be the most cost effective treatment only when the willingness to pay exceeds around £75,000 per QALY; below this, tacrolimus appears to be the most cost effective option.
Model provided?	Yes	
	Base case model	**Appropriate?**
Other considerations		Two versions of the model were provided by the company, both of which include multiway cost effectiveness acceptability curves (CEAC), but they present opposing results of the probabilities of cost effectiveness of ciclosporin and tacrolimus .

AWTTC = All Wales Therapeutics and Toxicology Centre; ECD = extended criteria donor; DCD = donation after cardiac death; GFR = glomerular filtration rate; AR = acute rejection; NODAT = new onset diabetes mellitus; PTLD = post transplant lymphoproliferative disorder; CUA = cost utility analysis; ICER = Incremental cost-effectiveness ratio; CEAC = Cost Effectiveness Acceptability Curve.

Table 1B. GFR states according to National Kidney Foundation Kidney Disease Outcomes Quality Initiative[20]

GFR stage	GFR (mL/min/1.73 m^2)
2	60–89
3a	45 – 60
3b	30 –45
4	15 –30
5	< 15